Strategy and Statistics in Clinical Trials

Presentation for a Workshop of

The Israel Statistical Organization

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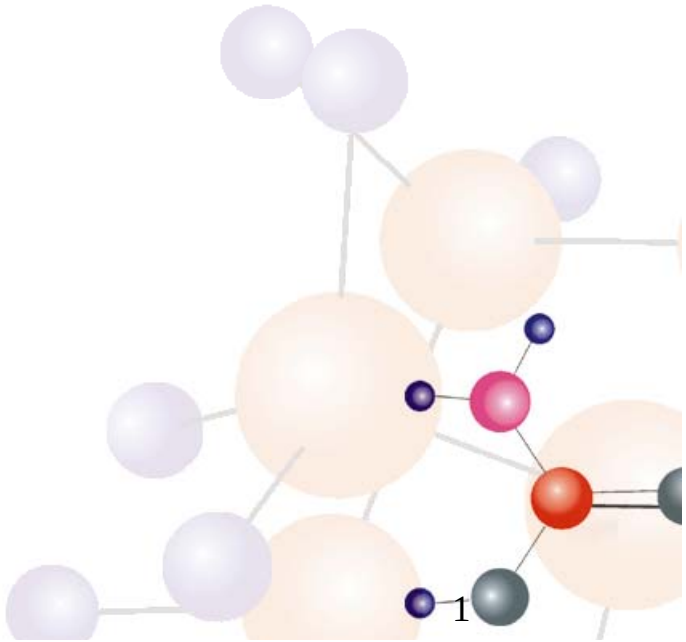


Clinical Trials as Multidisciplinary Efforts

*"When putting together a clinical trial, each discipline involved brings its own particular and peculiar view to the table. Some are complementary, while others combine less seamlessly. Still others pull in different directions. It is your job to find the best way to profit from this kaleidoscope of views—to merge the varying approaches to produce a solid study."**

- This short presentation will:
  - Tell a multidisciplinary story and describe some of the statistical aspects of it
  - Provide my view of some of a statistician's roles in trials, keeping in mind that:
    - This is *one* person's view
    - There are few absolutes in the process in any case

*Tal, J. *Strategy and statistics in clinical trials: a non-statistician's guide to thinking, designing, and executing*. Academic Press (Elsevier), Boston, Mass.: 2011

Background: EMA's "Orphan Designation"

- Drug companies work for a profit—they'll avoid developing drugs for rare diseases that provide little market potential
- Regulators have developed *orphan* designation criteria for such products
- Once designated "orphan," the process of drug development is shorter and less costly
- European Medicines Agency (EMA), qualifies a drug for orphan designation if:
  - Drug is for treatment, prevention or diagnosis of life-threatening or chronically debilitating disease
  - Prevalence in EU is 5 in 10,000 at most, or unlikely that product would generate sufficient returns to justify investment
  - No satisfactory method of diagnosis, prevention or treatment of the condition concerned can be authorized, or, if such a method exists, the medicine must be of significant benefit to those affected by the condition.

EMA(2013). Regulatory: Orphan designation. http://www.emea.europa.eu/ema/.

Background: FP7 and Trial

- Swiss/French company applies for European Union FP7 grant
- “Seventh Framework Program (FP7) bundles… research-related initiatives together”
- Company applies for FP7 grant for preventing an *Orphan Disease* we shall call OD, resulting from Condition X (CX)
- Aim: Phase II/III—A single trial for proof-of-concept & market authorization
- Design:
  - 3 arms: medium dose, high dose, placebo
  - Powered for superiority of both doses on single primary endpoint (E1)
  - Interim analysis
  - Overall N > 300 (~ 100 per group)—relatively large in orphan disease
- Company receives up to €6 mil on condition that it commit matching funds

Company and EMA (initial documents sent & TC for advice)

- **Company**: Prevention of OD resulting from CX is an orphan indication
  - **EMA:** OD can result from other than CX ➔ "prevention" is not orphan since drug can be given in a number of indications leading to OD
- **Company**: Goal is to demonstrate superiority on primary endpoint E1
  - **EMA:** E1 is pharmachodynamic, not clinical—additional endpoint E2 should be specified; trial should have co-primary endpoints
- **Company**: Molecule shown safe/effective in related indications, one Phase II/III trial for market authorization should be enough
  - **EMA**: Another trial will be needed; can't combine proof-of-concept and pivotal

- 1st bullet jeopardizes FP7 grant, which is for orphan indication only
- 2nd jeopardizes success, clinicians do not know if E2 can be shown
- 3rd bullet adds great expense for Company, jeopardizes project/indication

Company and Principal Investigator

- **Company**: Change indication from “prevention” to “treatment” of OD by including only those who already have the main symptom of the disease
  - **PI**: Once main symptom appears it’s too late ➔ argue for “prevention” w/EMA
    - **Company**: Prevention = no “orphan” ➔ no project. Must find solution.
- **PI**: Molecule may not be superior to Placebo on 2nd primary endpoint
  - **Company**: Must specify E1 *and* E2 for success, otherwise EMA won’t authorize
    - **PI**: Ok, no choice
- **Company**: Since 1 trial not enough ➔ limit size of this trial: 2-arm not 3 (high dose best anyway). Also time passed, grant is time-limited & recruitment’s difficult
  - **PI**: In one study, high dose was weaker than medium—must keep 3-arm trial; Also “we were funded for a large enough trial. Time extension is possible”.
    - **Company**: Medium dose better by chance. Besides, to sell molecule or get strategic partner, we need to show “sign of efficacy” only

Statistician & PI/Company: Prevention vs. Treatment

- **PI & Company**: Create viable "treatment" option (rather than "prevention")
  - **Statistician**: Not much to contribute here—sits and listens
- **PI** & **Company**:
  i. Little is known about disease—almost no research and vague definitions
  ii. Could we define disease earlier and say we are treating?
  iii. PI/opinion-leaders redefine "early OD" using more stringent inclusion criteria
  iv. Including only these patients means we are now "treating" not "preventing"
  - **Statistician**: This is actually a "classic" problem in diagnosis, where disease is on a continuum and the cutoff for absence/presence is not clear:
    - When there's a gold-standard reference (e.g. biopsy), no problem
    - No reference, so we have some freedom to determine cutoff
    - Use this argument to get EMA to at least agree that cutoff isn't obvious

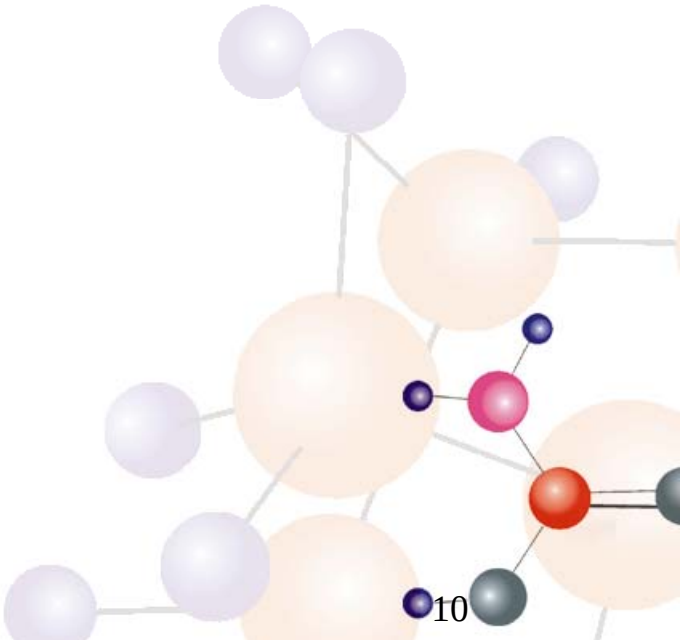
Statistician & PI/Company: Endpoints

- **PI** & **Company**: Define endpoint where subject is responder if E1 and E2 are absent, otherwise subject is non-responder
  - **Statistician**: But EMA wrote:
    - *"Given the Mechanism of Action, E1 could be considered a pharmacodynamic effect rather than the real effect looked for…an effect on E2 would be more convincing… Ideally a significant effect in both variables should be demonstrated as co-primary endpoints*
  - **Statistician**: EMA imply two co-primary, while company/PI define composite
- **PI**: But we may not be able to show superiority on E2 by itself
  - **Statistician**: How about demonstrating non-inferiority? After all,
    - E1 is very meaningful clinically
    - Molecule has better safety profile then existing (insufficient) treatments
- **PI** & **Company**: Ok—Superiority on E1 and non-inferiority on E2

Statistician & Company/PI: Sample Size

- **Company** vs. **PI**: Company wants drastically reduced sample size, suggests 2-arm instead of 3, and each arm with less. PI says at least original sample needed for dose-finding, and especially now with success on E2 required as well
  - **Statistician**: Are both doses about equally effective? **Company**: "Yes"
  - **Statistician**: If so, why not 3-arm trial where primary analysis combines the 2 doses vs. placebo? This way we have both dose-finding and 2-arm power
    - **PI**: But problem of power regardless—need original N
  - **Statistician**: Is effect size larger with new inclusion? **PI**: "Perhaps"
  - **Statistician**: If no longer pivotal ("sign of efficacy" enough), could one endpoint be continuous rather than responder/non-responder? **Company**: "Yes"
  - **Statistician**: Combine arms for primary analysis ("exposure") & specify continuous endpoint for E2➔ more power, smaller N

Questions

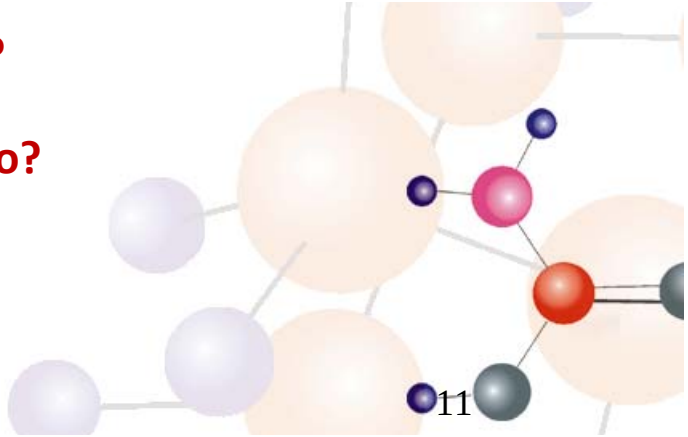


Before it all Begins

- A Clinical trial has implications for much, if not all, the organization
- Bio-statistics is involved in virtually all these activities. Examples:
  - Clinical: What is the optimal trial design? Which data to collect?
  - Regulatory: Which statistical tests are expected by the regulator?
  - Marketing: Can trial results attract buyers? Be published in good journal?
  - Finance: What are the implications of differing designs for cost? Should I look at the data in the interim to cut losses? How?
- Trial planning must involve a comprehensive Q&A process
- "How many subjects" is but one question. The more basic questions are:

WHAT do I want to show?

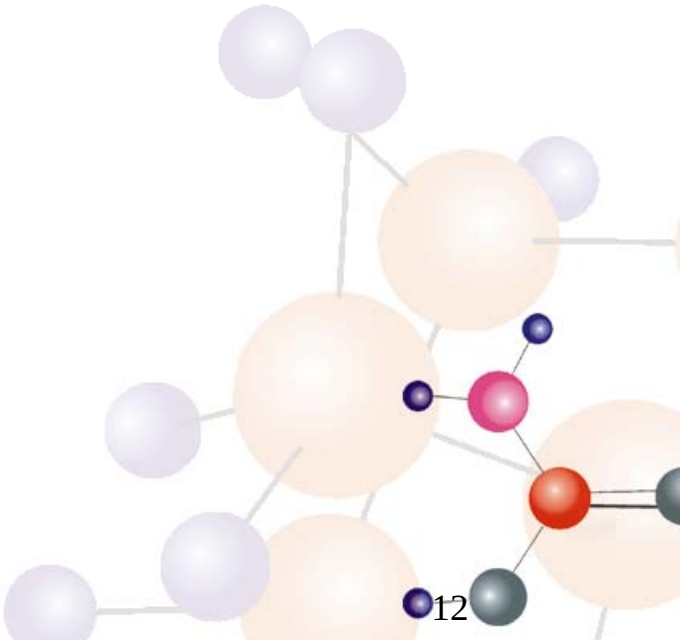
WHO do I want to show it to?



What do I Want to Show?

- On which attributes will my trial focus?
  - Efficacy
  - Safety
  - Pharmacokinetics

- For the relevant attributes, what do I wish to show?
  - Superiority
  - Equivalence
  - Non-inferiority
  - Dose-response, Dose-finding



Who do I Want to Show it to?

- Regulator
  - Which?
  - What does regulator expect from me? (Advice, Pre-IDE/IND)
- Investors: Present and/or future
  - What will convince investors? What are appropriate milestones?
- Internal: R&D, Clinical, Marketing, Regulatory…
  - What do each of these expect from this trial?
- Medical Community
  - What will convince the medical community? What do I need to do to publish in the journal(s) of my choice?


"That's all Folks!"